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LETTER TO THE EDITORS

Bifocal extradural cortical stimulation-induced recovery of consciousness in the permanent post-traumatic vegetative state

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To the Editor:

The chance of recovery from vegetative state (VS) 1 year after traumatic brain injury (TBI) is close to zero, i.e., it is permanent, PVS [5, 14]. Deep brain stimulation (DBS) of the midbrain or thalamus failed to improve awareness in PVS patients [15]. Yet, imaging studies suggest the potential for cognitive processing in a subset of patients and potentially recruitable cortical regions [6–9, 11]. Isolated thalamocortical "island" circuits may be working in PVS [6–9, 11]. We now find that bifocal, extradural cortical stimulation (b-ECS), a very safe minimally invasive surgical method [2–4], can restore conscious contents in the PVS. The present result differs from recent reports of an improvement of the minimally conscious state by DBS [13]: it is known that PVS and the MCS are different physiological entities, with large-scale "higher order" cortical activation on functional neuroimaging in MCS, normally not observed in PVS patients, a much better prognosis for the MCS even past 12 months, and sporadic, weak, inconsistent, but clearly intentional actions in MCS, but not PVS [9].

This female (born in 1988) was diagnosed as permanently vegetative following a car crash in January 2005. During the first week post-injury, her Glasgow Coma Scale was 5–6. She underwent right decompressive hemicraniectomy (with flap replaced at a later date) and went on to receive intensive neurorehabilitation for more than 1 year, to no avail. In August 2007, somatosensory evoked potentials (SSEPs) at the median nerve demonstrated absent N20/P25 components on both sides. Structural MRI showed a supratentorial right lateral ventricular enlargement due to scar retraction and signs of encephalomalacia on that side. On examination, the patient stared blankly in front of her, without any sign of visual pursuit. The defensive blink reflex was completely absent. Repeated verbal commands were not obeyed, even when given by familiar voices. Sporadic spontaneous movements of the four limbs were noted. Her head was often turned to the right, with the left arm flexed and her spastic left leg extended. Spastic retraction of the left arm was observed following nociceptive stimuli, with hyperextension of both legs. The patient was completely unable to localize external stimuli. She was scored 25 (category 9) on the Disability Rating Scale (DRS). This patient's parents gave surrogate informed consent to surgery after Inner Review Board approval. After induction of general anesthesia, a double, parallel, sigmoid incision of the skin overlying the target areas was performed in August 2007. The left side was elected, i.e., the side contralateral to her previous hemicraniectomy. The sulcus between the left parietal gyri P1 and P2 and the middle frontal sulcus (F2), including Brodmann's areas 8 and 46 (dorsolateral prefrontal cortex, DLPFC), were targeted under neuronavigation guidance. Four burr holes were fashioned, and two stimulating paddles were inserted extradurally (Lamitrode 4, ANS). The paddles were linked via a dual extension to a subclavearly pocketed pulse generator (IPG) (Genesis, ANS). One week post-surgery, stimulation was started simultaneously on both channels. Over the following 10 months, the patient was assessed by an independent third party who was totally blind to the procedure on nine occasions at 1-month intervals, after which parameters could be reset.

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Additionally, the patient was assessed thrice weekly by one member of the study. The Coma Recovery Scale-Revised (CRS-R) and the levels of cognitive functioning (LCF) were used to quantify clinical progression (Fig. 1). The CRS-R is a standardized behavioral rating scale comprised of six subscales designed to assess auditory, visual, motor, oromotor/verbal, communication, and arousal functions. Subscale items are arranged hierarchically in that the lowest item reflects reflexive activity and the highest item represents cognitively mediated behavior. Interrater and test–retest reliability for the CSR-R score is high. The scale has a high concurrent validity with the DRS, a well-established measure that gauges neurobehavioral responsiveness and functional capacity (see discussion in [13]).

Best settings were: active electrodes ++−−/−−++, 8–10 Hz, 65 μs, and 11 mA. Changes in arousal, tone and other vegetative parameters were observed within 12 h of rescheduling the programmer. Some parameters were less effective than others, but overall still provided scores higher than baseline. Shortly after initiation, vigilance increased, with clear improvements of swallowing and self-management of oral secretions. Oral feeding has become possible (she now opens the mouth without "cue touch"), without any opposition, and episodes of aspiration have not been reported. Currently, she is receiving three meals a day by mouth, and her diet includes solids. One month into the study, a brisk, repeatable defense blink reflex emerged for the first time. Vegetative functions (drooling, defecation, appetite, sleep, weight) all gradually improved, and the patient is now 4 kg heavier. Her facial mimic has changed toward a more normal pattern. Spontaneous movements of the limbs (more on the left) have become more conspicuous in time. Emotional facial reactions were observed well within the first month of stimulation, with appropriate fixation and smiling at familiar (but not other) faces. Several months into the study, the patient could obey the simple orders of raising her left hand and arm (see online video), generally in the afternoon. She now shows signs of visual pursuit and turns the head to the right. Her parents can stand her up without undue effort, due to improved axial tone. Vocalizations have been noted by family members. Spasticity improved. During the whole study period, the patient continued her physiotherapy at least twice a week. On several occasions, the patient was deemed "conscious and cooperative" by physical therapists. Ten months into the study, the batteries ran out: improvements were initially maintained, but after a few months, her ability to respond to simple orders dwindled. Her battery was then replaced, and within 1 month she reverted to the previous degree of improvement.

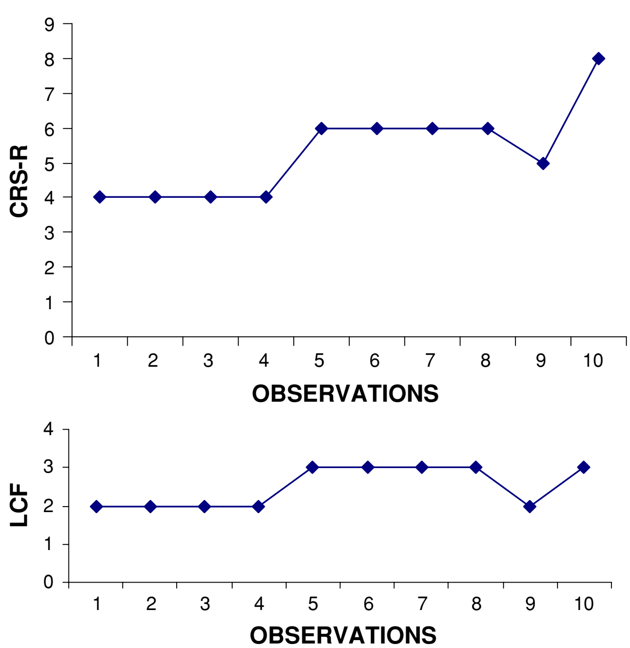

Fig. 1 *Graph* showing scores on the JFK Coma Recovery Scale-Revised (*CRS-R*) (Giacino et al. Arch Phys Med Rehab 85:2020–2029, 2006) and levels of cognitive functioning (*LCF*) (Hagen et al. Rancho Los Amigos Hospital, 1972) for each of the ten (basal + nine) evaluation sessions

Conscious response to simple orders has never been achieved by previous neurosurgical attempts in PVS cases. The clear-cut repeatability of the motor order makes such distinction robust. Spontaneous recovery is statistically unlikely: this patient has been in PVS for 20 months, well beyond the 1-year limit of possible expected recovery. Moreover, effects started soon after stimulation and changed acutely with parameters changes. Above all, clinical worsening was observed after a few months with stimulation off (a similar profile to what occurs during ECS for Parkinson's disease: battery change restored her previous level of benefit, indicating that continuous stimulation is necessary to maintain benefit.

The choice of target is explained by current understanding of consciousness-supportive networks. The most impaired network in imaging studies of the PVS is the frontoparietal network of polymodal associative cortices [1, 8, 10, 14]. Frontoparietal association areas (BA8/46 and the P1/2 region, i.e., the areas targeted in the current patient) have a special relationship with consciousness and may support a "self" system that is disrupted in PV [1, 10], making these a logical choice for stimulation. Stimulation of DLPFC, via its connections with the supplementary motor area (SMA), was also expected to influence swallowing and axial tone. We speculate that unilateral bifocal ECS marshalled isolated thalamocortical circuits [2, 3] and "resynchronized" them [2, 3, 12]. Unilateral ECS is known to recruit both hemispheres (via callosal and/or cortico-cortical connections) [2, 3] and also to induce poststimulation after-effects [2, 3]. ECS can also enhance neuroplasticity during stroke rehabilitation [4], by altering, among others, neurotransmitter levels in the brain [4].

In conclusion, we show for the first time that even the PVS can be targeted for neurostimulation, with expected reinstatement of at least some restricted periods of conscious and cooperative behavior.

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